INTRODUCTION

In the search for a new drug, three approaches are generally followed: (1) the general screening approaches in which chemical substances from any substances whose biological effects are known, (2) the chemical modification of existing drug substances whose biological effects are known and (3) mimicking the nature by biological design, where a compound is made to exert an action in a manner similar to a known biochemical substance. Any lead compound obtained from these three approaches is usually further modified chemically to gain the biologically most potent representative of the series.

Non steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medications in the world [1]. Traditional NSAIDs are used in treatment of mild to moderate pain and as an adjunct to opioids in the management of moderate to severe pain [2]. The clinical effects of $NSAID_S$ are based on the inhibition of the enzyme cyclooxygenase (COX), which catalyses the rate limiting step in the formation of prostanoids, thromboxane A and prostaglandins (PGs) [3, 4].

There are mainly two types of COX enzymes namely COX-1 and COX-2; COX -1 is a constitutive enzyme expressed in most tissues including blood platelets and is involved in tissue homeostasis. COX-2 is induced in inflammatory cells when they are activated. The primary inflammatory cytokines, interleukin-1 and tumor necrosis factor – alpha (TNF- α) are important in this regard. Thus COX-2 is responsible for the production of the prostanoids- the mediators of inflammation. Most traditional NSAIDs in current use are inhibitors of both isozymes[5].

A wide variety of heterocyclic compounds can serve as specific templates for COX-2 inhibitors like thiazoles, furans, thiophenes, pyrroles but, at the moment pyrazoles, cyclic ketones, indazoles and quinazolines seem to be the most appropriate tools for COX-2 specificity[6-8].

In recent years, microbial infections have been associated with rates of morbidity and mortality[9]. The resistance of common pathogens to standard antibiotic therapies is a major public health concern in the world, the incidence of multidrug resistant Gram-negative and Gram-positive bacteria is increasing and infections caused by them are becoming complex in recent years[10]. There is a real perceived need for the discovery of new compounds having antimicrobial activity, possibly acting through mechanisms of action, which are distinct from those of well known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant[11].

The azole antimicrobials may be regarded as a new class of drugs that inhibits microbes by blocking the biosynthesis of ergosterol, a major component of the microbial plasma membrane, by inhibiting the cytochrome P-450 dependent enzyme lanosterol demethylase.[12,13] These agents have dominated antifungal drug development and clinical use because of their broad spectrum, oral bioavailability and low toxicity[14]. Systemic fungal infections are life threatening and have become increasingly common in the immune compromised hosts[15].

Hexahydroindazole, a novel heterocyclic compound has been reported to have antimicrobial[16,17] and anti- inflammatory activities[6]. Heterocyclic quinazoline derivatives possess various biological activities *viz*. anticonvulsant[18], antiphlogistic[19], muscle relaxant[20], antimalarial[21] and antihistaminic[22] activities. Quinazolines, especially octahydroquinazolines have been reported to possess antimicrobial activity against different pathogenic microorganisms[23].

Microbial infections often produce pain and inflammation. In normal practice, the chemotherapeutic, analgesic and anti-inflammatory agents are prescribed concomitantly. There are effective antimicrobial agents in the market, but each drug carries several drawbacks. The presently marketed antimicrobial drugs are either toxic or becoming ineffective due to the appearance of resistant strains, which requires prolonged administration of the available antimicrobial agents[24, 25].

This concept of multidrug therapy has dual advantages in not only reducing the number of drugs to be taken at a time but also that the side effects due to multi drug therapy shall be lessened.

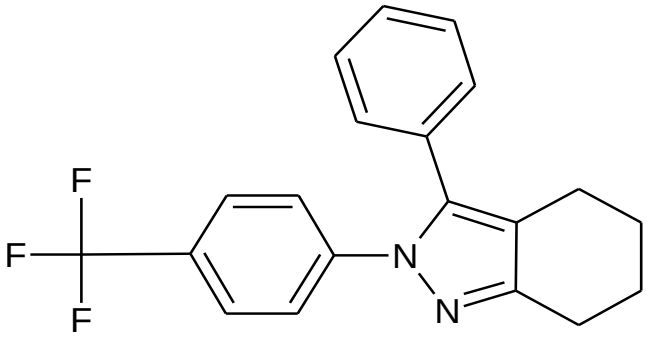
Quantitative structure activity relationship (QSAR), as one of the most important areas in chemistry gives information that is useful for designing new drugs. These are mathematical equations relating chemical structure to a wide variety of physical, chemical, biological activities used to estimate the property of other molecules and to find the parameters affecting the biological activity.[26]

The literature survey has revealed only a limited Quantitative Structure Activity Relationship (QSAR) information[27,28] correlating the structure of hexahydroindazoles and octahydroquinazolines with their biological activities.

LITERATURE REVIEW:

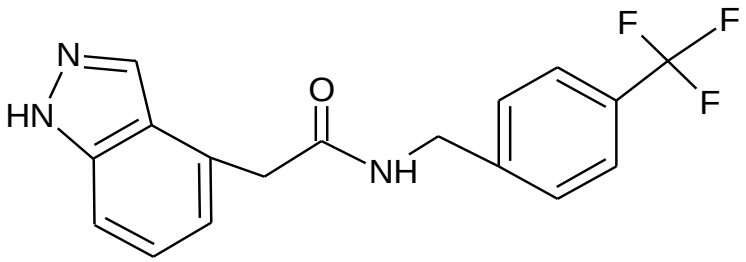
INDAZOLES AS ANTI-INFLAMMATORY AND ANALGESIC AGENTS

Some new 2, 3 – disubstituted tetrahydro- 2*H* – indazoles were synthesized and screened for their *in vivo* evaluation in two different experimental models (Freund's adjuvant-induced arthritis and Carrageenan-induced edema). The compound 3- phenyl- 2-[4-(trifluoromethyl) phenyl]-4,5,6,7-tetrahydro-2*H*- indazole **(1)** showed to possess high anti-inflammatory activity along with the lack of gastric injury even at high doses in gastric ulcerogenic assays[29].



(1)

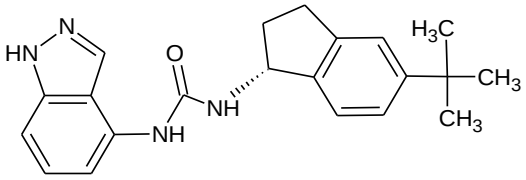
Investigations on biological activity of novel 5,6- fused heteroaromatic benzyl ureas have shown that the compound containing the indazole core and 3,4-dichlorophenyl group appended to it via a urea linker 2-(1*H*-indazol-4- yl)-N -(4-trifluoromethylbenzyl) acetamide **(2),** demonstrated *in vivo* analgesic activity upon oral administration. Large electron- withdrawing groups, such as CF_3, OCF_3 and 3, 4-diCl, in the benzyl portion of the molecule afforded the most potent compounds *in vitro* [30].



(2)

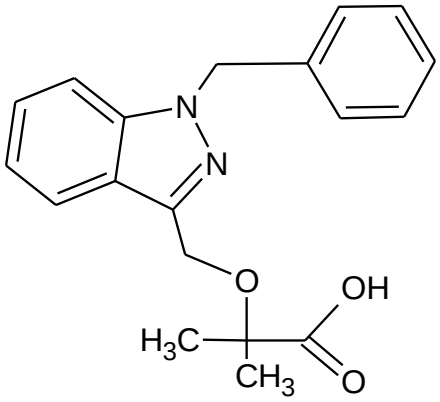
Vanilloid receptor TRPV1 is a cation channel that can be activated by a wide range of noxious stimuli, including capsaicin, acid and heat. Blockade of TRPV1 activation by selective antagonists is under investigation by several pharmaceutical companies in an effort to identify novel agents for pain management. The replacement of substituted benzyl groups by an Indan rigid moiety in a previously described N –indazole-N'-benzyl urea series led to a number of

TRPV1 antagonists with significantly increased *in vitro* potency and enhanced drug like properties. Extensive evaluation of pharmacological, pharmacokinetic, and toxicological properties of synthesized analogs resulted in identification of *(R)* -1-(5-*tert*-butyl-2, 3-dihydro-1*H*-inden-1-yl)-3-(1*H*-indazol-4-yl) urea (ABT-102, **3**), which possess good analgesic activity [31].



(3)

Chemokines are believed to play a key role in the pathogenesis of acute pancreatitis and the pancreatic acinar cells produce the chemokine, Monocyte Chemotactic Protein (MCP)-1 in response to caerulein hyperstimulation, demonstrating that acinar derived MCP-1 is an early mediator of inflammation in acute pancreatitis. Blocking chemokine production or action is a major target for pharmacological intervention in a variety of inflammatory diseases, such as acute pancreatitis. Bhatia *et al.* [32] investigated the effect of 2-methyl -2-[[1-(phenylmethyl)-1*H* indazol-3yl] methoxy] propanoic acid (Bindarit, **4**) on MCP-1 levels in acute pancreatitis.



(4)

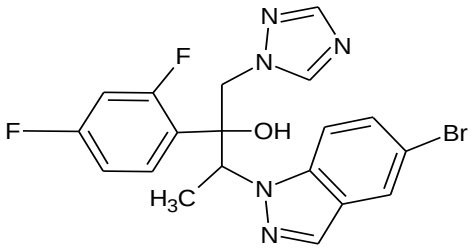
They observed that in a model of acute pancreatitis induced by caerulein hyperstimulation, prophylactic as well as therapeutic treatment with **4** significantly reduced MCP-1 levels in the pancreas. Also, this treatment significantly protected mice against acute pancreatitis.

INDAZOLES AS ANTIMICROBIAL AGENTS

The search for new antimicrobials in recent years has concentrated principally on the indazoles and its related area of chemistry.[33] The group of drugs known collectively as the azoles, comprising a number of 1 and 2-substitued indazole compounds undoubtedly represent the

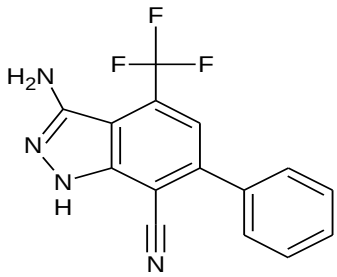
modern approach to both topical and systemic treatment of antibacterial and antifungal diseases. The azole antifungal agents have pronounced pharmacological and biochemical activities.

A series of (2*R*, 3*R*)-2-(2, 4-difluorophenyl)-3-(substituted indazol-1-yl)-1-(1*H*-1, 2, 4-triazol-1-yl) butan-2-ol were synthesized and screened for their antifungal activity. In particular, the compound 3-(5-bromo-indazol-1-yl)-2-(2,4-difluorophenyl)-1-[1,2,4]-triazol-1-yl-butan-2-ol **(5)** exhibited significant antifungal activity against a variety of fungal cultures *(Candida* spp. and A*spergillus* spp.*).* In addition, oral administration of **5** showed its excellent efficacy against *Candida albicans* in a murine infection model and the significantly improved survival rates of the infected mice.[34]



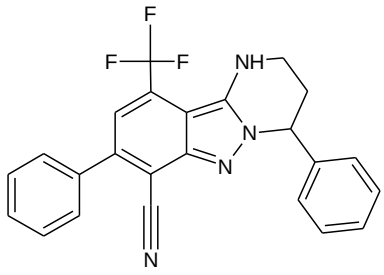
(5)

Indazole regioisomers such as 3-amino-4-(trifluoromethyl)-6-phenyl-1*H*-indazole-7-carbonitrile and 3-amino-6-(trifluoromethyl)-4-phenyl-1*H*-indazole-7-carbonitrile[35] were independently reacted with formaldehyde followed by unsymmetrical, symmetrical and cyclic electron rich olefins in presence of $GdCl_3$ as catalyst to yield pyrimidine fused indazole derivatives respectively.



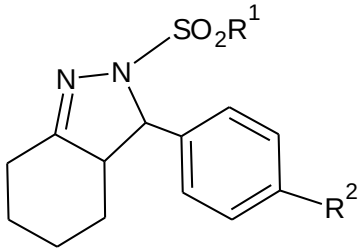
(6)

The synthesized compounds were screened against Gram-positive, Gram-negative bacteria andfungal species such as yeast and filamentous fungi *in vitro*. The compound **6** showed potent activity with reference to Penicillin as well as streptomycin. Similarly compound, 4, 8-diphenyl-10-trifluoromethyl-1,2,3,4,-tetrahydropyrimido[1,2-b]-indazole-7-carbonitrile **(7)** showed promising activity against yeast and filamentous fungi.[35]



(7)

Minu *et al.*[36] synthesized a series of 2, 3-disubstituted-3, 3a, 4, 5, 6, 7-hexahydro-2*H*-indazoles **(8)**, which were evaluated for their *in vitro* antimicrobial activity by the tube dilution method. It was seen that Compounds having electron withdrawing groups like *p*-fluorophenyl groups improved the antibacterial activity while *p*-chlorophenyl groups improved the antifungal activity.



(8)

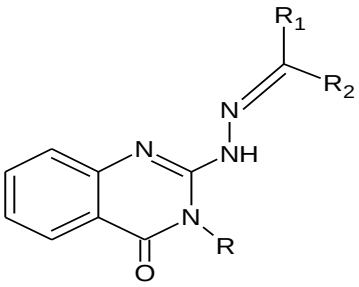
BIOLOGICAL SIGNIFICANCE OF QUINAZOLINES AND RELATED COMPOUNDS

Quinazolines and related compounds have been associated with various biological properties, ranging from anti-inflammatory[6], antimicrobial[16-17], antihistaminic[22], anticancer, anticonvulsant[18], antitubercular[16] activity.

QUINAZOLINES AS ANTI-INFLAMMATORY AND ANALGESIC AGENTS

Various quinazoline derivatives have been synthesized and their anti-inflammatory and analgesic activities have been investigated. A variety of novel 3-(4-methoxyphenyl)-2-substituted-aminoquinazolin-4-(3*H*)-ones (**9-15**) were synthesized by reacting the amino group of 2-hydrazino-3-(4-methoxyphenyl)-quinazolin-4-(3*H*)-one with a variety of alkyl and aryl ketones. These were investigated for analgesic, anti-inflammatory and ulcerogenic index activities.

The compounds 2-(1-methylpropylidene) **(9),** 2-(1-ethylpropylidene) **(10)** and 2-(1-methyl butylidene) **(11)**- hydrazino-3-(4-methoxyphenyl)quinazolin-4-(3*H*)-one derivatives showed moderately more potent analgesic activity, while the compound **(10)** showed moderately more potent anti-inflammatory activity than the reference standard Diclofenac sodium[37].



9) R =*p*-$OCH_3C_6H_4$ R_1 =CH_3 R_2 =C_2H_5

(10) R =*p*-$OCH_3C_6H_4$ R_1 =C_2H_5 R_2 =C_2H_5

(11) R =*p*-$OCH_3C_6H_4$ R_1 =CH_3 R_2 =$CH_2CH_2CH_3$

(12) R =C_6H_5 R_1 =CH_3 R_2 =C_2H_5

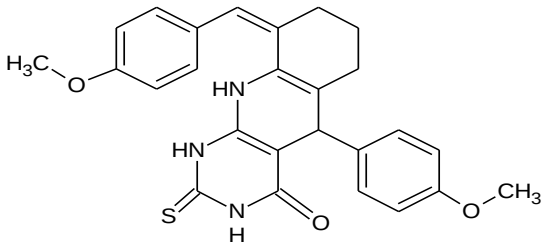
(13) R =C_6H_5 R_1 =C_2H_5 R_2 =C_2H_5

(14) R =C_6H_5 R_1 =CH_3 R_2 =$CH_2CH_2CH_3$

(15) R =C_6H_4N R_1 =CH_3 R_2 =$CH_2CH_2CH_3$

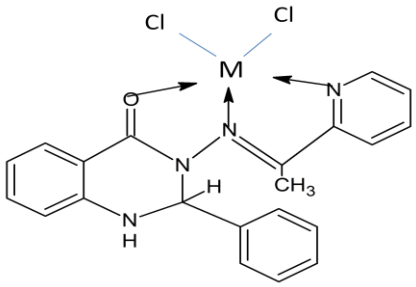
Similarly, compounds, 2-(N'-2-butylidenehydrazino)- **(12),** 2-(N'-3- pentylidenehydrazino)-**(13),** 2-(N'-2-pentylidenehydrazino)- **(14)** and 2-(1-methylbutylidene)hydrazine **(15)** 3-(2-pyridyl)quinazoline-4-(3*H*)-one derivatives have been reported to have better analgesic, anti-inflammatory potential than the Diclofenac sodium.[38 39]

Baraka reported the synthesis of novel 2, 4-(1*H*, 3*H*)-quinazolinedione derivatives as potential analgesic and anti-inflammatory agents.[40] Another category of quinazolinones was synthesized and tested for their anti-inflammatory activity. The compound, 5-(4-methoxyphenyl)-9-(4-methoxyphenylmethylene)-5,10-dihydro-2-thioxo-6,7,8,9-tetrahydropyrimido-[4,5-b]-quinaz-olin -4-one **(16)** exhibited a potent anti-inflammatory activity in carrageenan-induced paw edema test in rats[41].



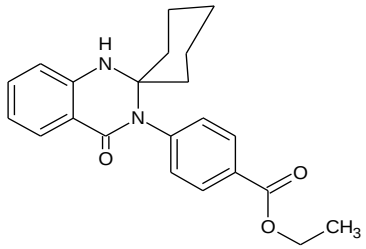
(16)

Five-coordinate neutral transition metal complexes of 3-aryl-2-substituted 1, 2-dihydroquinazolin-4(3*H*)-one **(17)** derivatives were synthesized and characterized by Hoonur *et al.*[42] and were tested for anti-inflammatory & analgesic activities. The transition metal complexes were found to be more active than the free ligand.



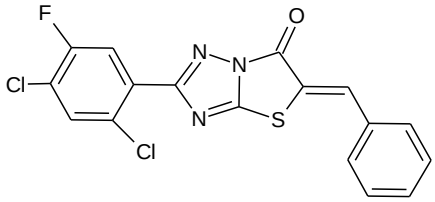
(17)

Amin *et al*[43]. synthesized a series of spiro-[(2H,3H)quinazoline-2,1- cyclohexan]- 4(1H)-one derivatives **(18)**. The derivative containing 4-(N, N-dimethyl)-2-hydroxyphenyl groups novel quinazolinone derivatives showed considerable anti-inflammatory and analgesic activity.



(18)

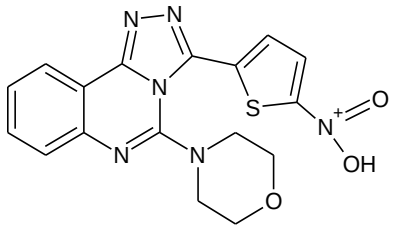
Mari *et al*[44] synthesized a series of 2,4-dichloro-5-fluorophenyl substituted arylidenetriazolo-thiazolidinones **(19)**. Compounds with 4-anisyl, 4-methylthiophenyl, 3,4-methylene-dioxyphenyl, and 2,3,5-trichlorophenyl moieties showed excellent antimicrobial activity.



(19)

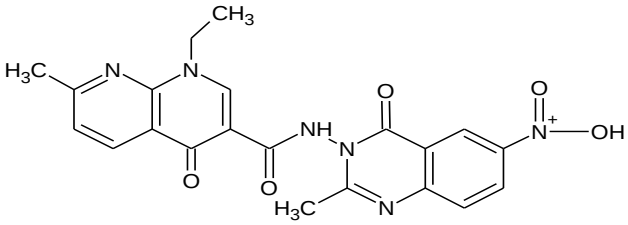
QUINAZOLINES AS ANTIMICROBIAL AGENTS

The antimicrobial activity of some substituted triazoloquinazolines has been studied and it was noted that the broadest antimicrobial activity resides with 5-morpholin-4-yl-3-(5-nitrothien-2-yl)-[1,2,4]-triazolo-[4,3-*c*]-quinazoline **(20)** in concentration of 10 mg/L for *B. subtilis*, 50 mg/L for *S. aureus* and 100 mg/L for *C. tropicalis.* The highest tested concentration of derivative caused 83% growth inhibition of *R. nigricans*[45].



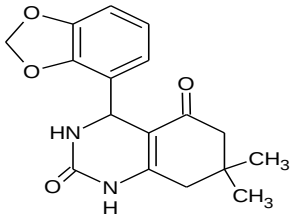
(20)

A series of new nalidixic acid derivatives having quinazolines moiety were synthesized and studied for their *in vitro* antimicrobial activity by Grover and Kini[46]. The derivative, 1-ethyl-7-methyl-4-oxo-1,4-dihydro-[1,8]-naphthyridine-3-carboxylicacid-(2-methyl-6-nitro-4-oxo-4*H*-qui-nazolin-3-yl)amide **(21)** showed marked inhibitory activity against enteric pathogen *Aeromonas hydrophila*, a causative agent of diarrhoea, respiratory pathogen S*treptococcus pyogenes, Candida* colonies and *Candida albicans*, when compared to standard Ampicillin and Fluconazole respectively. The derivatives showed decreased inhibitory activity against *Proteus vulgaris* and no significant inhibitory activity against *coagulase* negative *Staphylococcus.*[46]



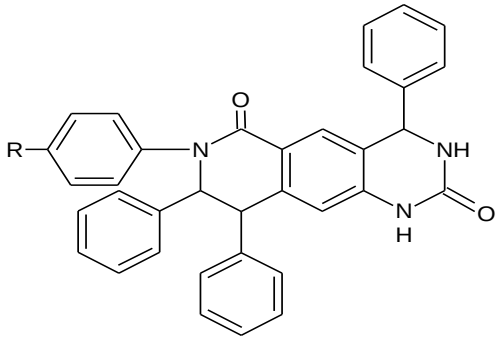
(21)

A series of 4-aryl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2- one/thione-5-ones were synthesized and screened for *their in vitro* antibacterial activity against standard strains of *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. Compound, 4-benzo-[1,3]-dioxol-4-yl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione **(22)**, showed potent antibacterial activity in comparison with Norfloxacin[47].



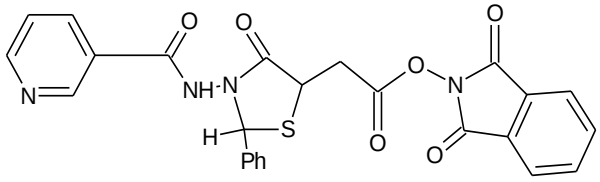
(22)

Tiwari *et al*.[48] reported simple, high yielding synthesis and *in vitro* study of novel pyrido-quinazolone analogues as anti-fungal and antibacterial agents. The compounds,4,6,7-triphenyl-8-(1-vinyl propenyl)-4,6,7,8-tetrahydro-1*H*,3*H*-1,3,6-triaza anthracene-2,5-dione **(23)** and 6-(4-chlorophenyl)-4,7,8-tripheyl-4,6,7,8-tetrahydro-1*H*,3*H*-1,3,6-triazaanthracene-2,5-dione **(24)** showed good antimicrobial activity against *Staphylococcus aureus*, *Aspergillus flavus* and *Aspergillus niger*.



(23) R=H **(24)** R = Cl

Joshi *et al.*[49] synthesized imido esters of 2-aryl-3-nicotinamido-4-oxothiazolidine ethanoic acid, **(25)** containing 3 active pharmacophores, niacin, thiazolidine & N-hydroxypthalimide in a single



(25)

nucleus framework. Final compounds showed moderate to good antibacterial activity against *E.coli, S. typhi, P.aeruginosa* and good antifungal activities against *C. albicans* & *A. fumigates*.

PLAN OF WORK:

With this background, we plan to synthesize the derivatives of hexahydroindazoles and octahydroquinazolinethiones bearing both electron donating and electron attracting substituents in para position of the sulfonylaryl moiety, characterize them and explore their biological potential and QSAR studies under the following heads:

a) Synthesis of substituted hexahydroindazoles and substituted octahydroquinazolines by appropriate synthetic procedures:

i) Synthesis of substituted hexahydroindazoles

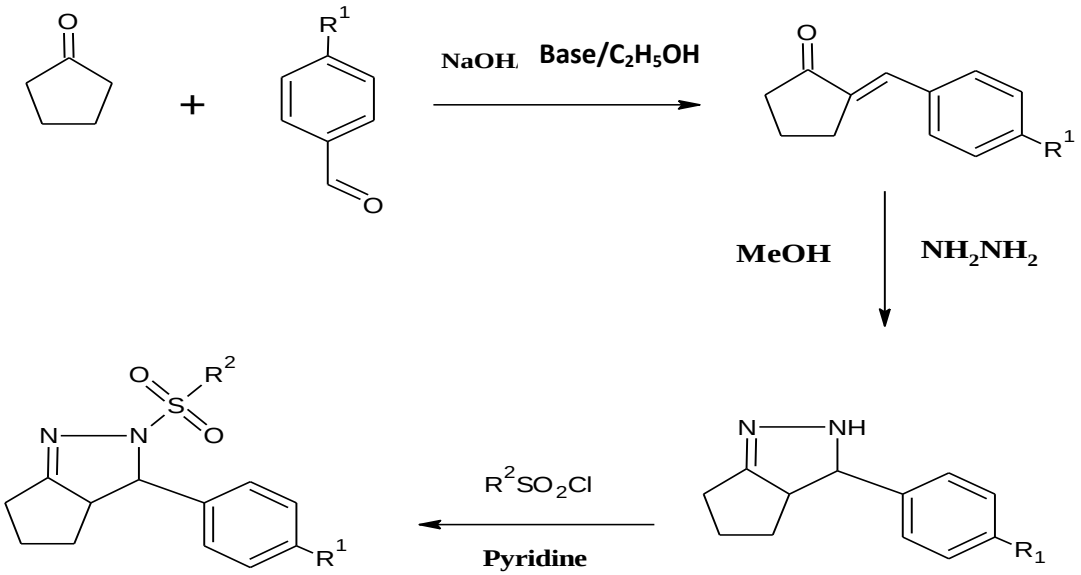
The hexahydroindazoles derivatives will be synthesized by the reaction of cyclopentanone and *p*-substituted aromatic aldehydes (p-chlorobenzaldehyde, p-fluorobenzaldehyde, p-methoxybenzaldehyde, p-nitrobenzaldehyde, 2,5-dichlorobenzaldehyde, etc) in the presence of a base by using conventional Claisen-Schmidt condensation[50]. The resulting benzylidene cyclopentanones will be heated with hydrazine hydrate in a Michael type of addition[51] reaction to yield 3-substituted hexahydroindazoles . This will be followed by sulfonation[52] with substituted sulfonylchlorides (like methanesulphonyl chloride, benzenesulphonyl chloride, 4-nitrobenzenesulphonyl chloride, 4-toluenesulphonyl chloride), in pyridine under different reaction conditions to yield the desired products i.e.2,3-disubstituted-3,3a,4,5,6,7-hexahydro-2*H*-indazoles **(Scheme-1).**

(ii) Synthesis of substituted-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thiones

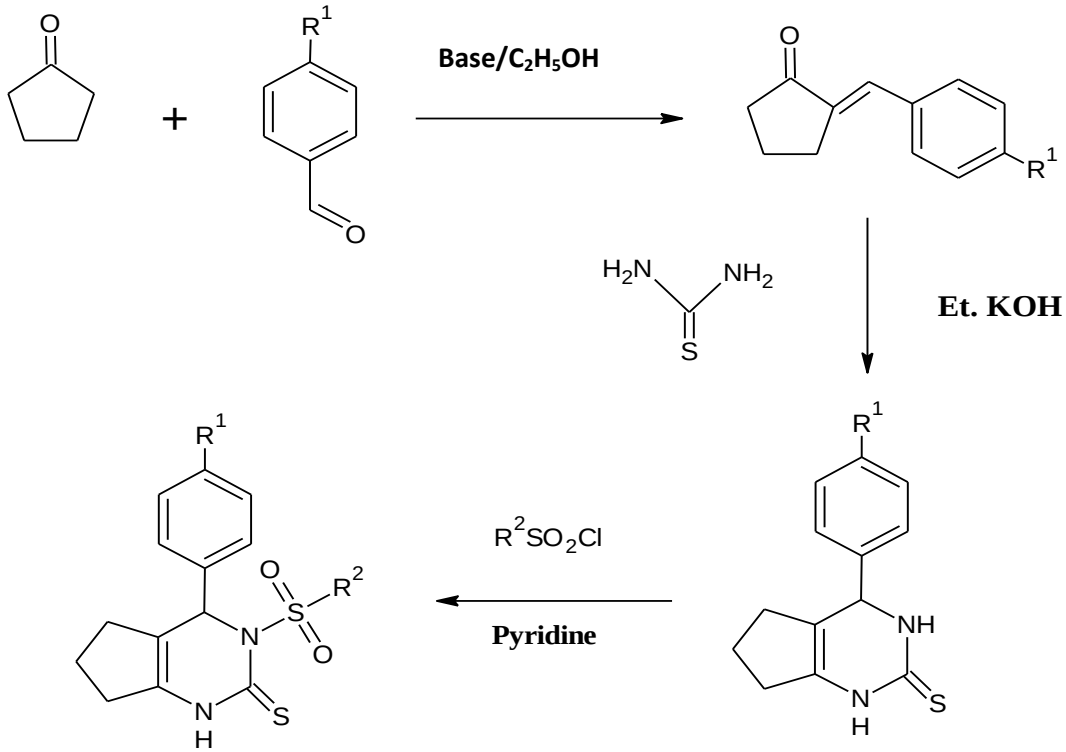
The different octahydroquinazoline derivatives will be synthesized by the reaction of cyclopentanone and *p*-substituted aromatic aldehydes (like p-chlorobenzaldehyde, p-fluorobenzaldehyde, p-methoxybenzaldehyde, p-nitrobenzaldehyde, 2,5-dichlorobenzaldehyde, etc) in the presence of a base using the Claisen-Schmidt condensation[50]. The resulting benzylidene cyclohexanones will be reacted with thiourea in alkaline condition[51] followed by acylation with substituted sulfonylchlorides[52] methanesulphonyl chloride, benzenesulphonyl

chloride, 4-nitrobenzenesulphonyl chloride, 4-toluenesulphonyl chloride), in presence of pyridine under different reaction conditions to yield the title compounds **(Scheme-2).**

SCHEME-1:



SCHEME-II:



Another series using the starting ketone as Cycloheptanone can also be synthesized yielding another series of the hexahydroindazoles and octahydroquinazoline derivatives.

2. **Physicochemical and spectral characterization of synthesized compounds:**

The purity of the synthesized compounds will be characterized by determination of melting points, R_f values; and their structures would be characterized with the help of Thin Layer Chromatography, UV-Visible spectroscopy, Infrared Spectroscopy (FT-IR), ^{1}H-NMR spectroscopy and Mass spectroscopy. Their log P values will also be calculated using octanol/water.

3. **Pharmacological studies:**

(a) The synthesized Hexahydroindazolines and Octahydroquinazolines will be evaluated for their *in vivo** anti-inflammatory activity and analgesic activities [53,54] .

(b) Evaluation of *in vitro* antibacterial and antifungal activities against the appropriate strains of microorganisms will also be carried out.

*All experimental protocols involving the use of animals need to be reviewed by the Institutional Animal Ethics Committee (IAEC) which should be constituted as per the guidelines of "Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA)", Government of India. Accordingly, a proposal can be submitted for constituting this committee for our institute and the activity studies can be carried out here.

If it is not possible,the *in vivo* activity studies would be carried out at the Pharmacology Division, Delhi Institute of Pharmaceutical Sciences and Research (DIPSAR), University of Delhi.

4. **Quantitative Structure Activity Relationship (QSAR) studies:**

In order to determine the correlation between the structural features of hexahydroindazole and octahydroindazole derivatives and their anti-inflammatory, analgesic and antimicrobial activities , QSAR studies will be carried out using the QSAR software.

REFERENCES

1. Botting, J. H. **Drugs Today** *1999*, 35, 225.
2. World Health Organization, **Cancer pain relief with a guide to opioid availability**, 2nd Ed.; W.H.O.: Geneva, *1996.*
3. Vane, J. R. **Nature** *1971*, 231, 232.
4. Busson, M. **J. Int. Med. Res**. *1986*, 14(2), 53.
5. Vane J. R.; Botting, R. M**. Therapeutic roles of selective Cox-2 inhibitors**, William Harvey press: London, *2001*; p 584.
6. Nasr, M. N.; Said, S. A. **Arch. Pharm**. **(Weinheim)** *2003*, 336(12), 551.
7. Wakitani, K.; Tazaki, H.; Matsushita, M.; Iwamura, H. **Inflamm. Res**. *2000*, 49, 117.
8. Dannhardt, G.; Kiefer, W. **Eur. J. Med. Chem**. *2001*, 36, 109.
9. Zanatta, N.; Alves, S. H.; Coelho, H. S.; Borchhardt, D. M.; Santurio, J. M.; Bonacorso, H. G.; Martin, M. A. P. **Bioorg. Med. Chem. Lett**. *2007*, 15, 1947.
10. Nezhad, A .K.; Rad, M. N. S.; Mohabatkar, H.; Asrari, Z.; Hemmateenejad, B. **Bioorg. Med**. **Chem**. *2005*, 13, 1931.
11. Antolini, M.; Boaaoli, A.; Ghiron, C.; Kennedy, G.; Rossi, T.; Ursini, A. **Bioorg. Med. Chem**. Lett. *1999*, 9, 1023.
12. White, T. C.; Marr, K.A.; Bowden, R. A. **Clin. Microbiol. Rev.** *1998*, 11, 382
13. Denning, D. W.; Kibler, C. C.; Barnes, R.A. **Lancet Infect. Dis**. *2003*, 3, 230.
14. Brunton, L. L.; Lazo, J. S.; Parker, K. L. **In Goodman and Gilman's-The pharmacological**
    Basis of Therapeutics, 11th Ed.; McGraw Hill New York, *2006*; p 1225
15. Liu, P.; Zhu, S.; Li, P.; Xie, W.; Jin, Y.; Sun, Q,; Wu, Q.; Sun, P.; Zhang, Y.; Yang, X.; Jiang, Y.;
    Zhang,D. **Bioorg. Med. Chem. Lett.** *2008.* 1; 18(11), 3261.
16. Raikova, S.V . Shub, G. M.; Luneva, I. O.; Golikov, A. G.; Bugaev, A. A**. Kriven'ko A. P. Antibiot**. **Khimioter.** *2005*, 50(2-3), 18.
17. Raikova, S. V.; Shub, G. M.; Golikov, A. G.; Kriven'ko A .P. **Antibiot. Khimioter**. *2004*, 49(4), 21.
18. Mannschreck, A.; Kollar, H.; Stunier, G.; Davies, M. A.; Traber, J. **Eur. J. Med. Chem**. *1984*, 19, 381.
19. Bekhit, A. A.; Habib , N. S.; el-Din, A.; Bekhit, A. **Boll. Chim. Farm**. *2001*, 140(5), 297.
20. Ochiai, T.; Ishida, R. **Jpn. J. Pharmacol.** *1982*, 32, 427.
21. Alagarsamy, V.; Giridhar, R.; Yadav, M.R. **J. Pharm. Pharmacol**. *2006*, 58 (9), 1249.
22. Alagarsamy, V.; Solomon, R.; Murgan, M. **Bioorg. Med Chem.** *2007*. 15, 400

23. Lopez, S. E.; Rosales, M. E.; Canelon, C. E.; Valverode, E. A.; Narvaez, R. C.; Charris, J. E.; Giannini, F. A.; Enriz R. D.; Carrasco, M.; Zacchino, S. **Hetrocycl. Commun**. *2000*,47,1279.
24. Fostel, I. M.; Lartey, P. A. **Drug Discovery Today.** *2000*, 5, 25.
25. Emami, S.; Farahyar, S.; Falahati, M.; Lotfali, E.; Rajabalian, S.; Ebrahimi, S. A.; Farahyar, S.; Sahfiee, A. **Bioorg. Med. Chem**. Lett. *2008*, 18, 141.
26. Agrafiotis, D. K.; Bandyopadhyay, D.; Wegner, J. K.; Vilijmen, H. V**. J. Chem. Inf. Model.** *2007*, 47, 1279.
27. Takami, A.; Iijima, H.; Iwakubo, M.; Okada, Y. *2001*,US2004/0102437 A1.
28. Takami, A.; Iwakubo, M.; Okada, Y.; Kawata, T.; Odai, H.; Takahashi, N.; Shindo, K.; Kimura, K.; Tajami, Y.; Miyake, M.; Fukushima, K.; Inagaki, M.; Amani, M.; Kaibuchi, K.; Iijima, H. **Bioorg. Med. Chem**. *2004*, 14, 2155.
29. Rosati, O.; Curini, M.; Marcotullio, M. C. ; Macchiarulo, A.; Perfumi, M. ; Mattioli, L. ; Rismondo, F. ; Cravotto, G. **Bioorg. Med . Chem**. *2007*, 15, 3463.
30. Drizin, I.; Gomtsyan, A.; Bayburt, E.K.; Schmidt, R. G.; Zheng, G. Z.; Perner, R. J.; DiDomenico, S.; Koenig, J.R.; Turner. S. C.; Jinkerson, T. K.; Brown, B. S.; Keddy, R. G.; McDonald, H. A.; Honore, P.; Wismer, C. T.; Marsh, K. C.; Wetter, J. M.; Plokowski, J. S.; Segreti, J.A.; Jarvis, M. F.; Faltynek, C.R.; Lee, C.H**. Bioorg. Med. Chem**. *2006*, 15(14), 4740.
31. Gomtsyan, A.; Bayburt, E. K.; Schmidt, R. G.; Surowy, C. S. ; Honore, P. ; Marsh, K. C.; Hannick, S. M. ; McDonald, H. A.; Wetter , J. M.; Sullivan , J. P.; Jarvis, M. F.; Faltynek, C. R.; Lee, C. H. **J. Med. Chem**. *2008*, 51(3), 392.
32. Bhatia, M.; Ramnath, R. D.; Chevali, L.; Guglielmotti, A. **Am. J. Physiol. Gastrointest. Liver. Physiol**. *2005*, 288(6), 1259.
33. Raikova, S. V.; Shuv, G. M.; Luneva, I. O.; Golikov, A. G.; Bugaev, A. A.; Krivel'ko ,A. P**. Antibiot**. **Khimioter**. *2005*, 50(2-3), 18.
34. Park, J. S.; Yu, K. A.; Kang, T. H.; Kim, S.; Suh, Y. G**. Bioorg. Med. Chem**. Lett. *2007*, 17, 3486.
35. Yakaiah, T.; Lingaiah, B. P. V.; Naraiah, B.; Kumar, K. P.; Murthy, V. S. N. **Eur. J. Med. Chem.** *2008*, 43, 341.
36. Minu, M.; Thangadurai, A.; Wakode,S. R.; Agarwal, S.; S. Narasimhan, B. **Bio.& Med**. **Chem**. **Lett.** *(2009*),19, 2960.

37. Alagarsamy, V.; Murugesan, S. **Chem. Pharm. Bull**. *2007*, 55(1), 76.
38. Alagarsamy, V.; Raja Solomon, V.; Dhanabal, K. **Bioorg. Med. Chem**. *2007* 15(1), 235.
39. Alagarsamy, V.; Solomon, R.; Murugan, M.; Sankaranarayanan, R,; Periyasamy, P.; Deepa, R.; Anandkumar, T.D. **Biomed. Pharmacother**. *2006*, 1.
40. Baraka,M. M. **Boll. Chim. Farm.** *2001*, 140(2), 90.
41. Alagarsamy, V.; Solomon, R.; Murugan, M.; Sankaranarayanan, R.; Periyasamy, P.; Deepa, R.; Anandkumar, T.D**. Biomed. Pharmacother**. *2006*, 1.
42. Hoonur, R. S.; Patil , B.R.; Badiger, D. S.; Vadavi, R. S. ; Gudasi, K. B.; Dandawate, P. R.; Ghaisas, M. M. ; Padhye, S.B. ; Nethaji, M**. Eur j. Medicinal Chem**. *2010*, 45, 2277.
43. Amin, K. M.; Kamel, M. M.; Anwar, M. M.; Khedr, M.; Syam, Y. M**. Eur J. Medicinal Chem**. *2010*, 45. 2117.
44. Mari, S.K.; Holla, B. S. **Monatsh Chem**. *2008*,139, 691.
45. Jantova, S.; Ovadekova, R.; Letasiova, S.; Spirkova, K.; Stankovsky, S. **Folia Microbiol**. *2005*, 50(2), 90.
46. Grover, G.; Kini, S. G**. Eur. J. Med. Chem**. *2006*, 41(2), 256.
47. Kidwai, M.; Saxena, S.; Khan, M. K. R.; Thukral, S. S. **Eur J. Med. Chem**. *2005*, 40, 816.
48. Tiwari, A.K.; Mishra, A.K.; Bajpai, A.; Mishra, P.; Sharma. R.K; Pandey, V.K.**;** Siingh, V.K. **Bioorg. Med. Chem. Lett.** *2006*, 16(17), 4581.
49. Joshi, A.; Sain, D.; Sharma, C.; Sharma, S.; Talesara, G**. Int. J. Chem. Sci**. 6(3), *2008*, 1684.
50. Kabli, R. A.; Kaddah, A. M.; Khalil, A.M.; Khalaf, A. A. **Indian J. Chem.** *1986*, 25B,152.
51. Khalaf, A. A.; El-Shafei, A. K.; El-Sayed, A. M. **J. Heterocyclic. Chem.** *1982*, 19, 609.
52. Sayed, G. H. **Indian J. Chem.** *1980*, 19B, 364.
53. Winter, C. A.; Risley, E. A.; Nuss, G. **Exp. Biol. Med.** *1962*, 111, 544.
54. Koster, R.; Anderson, M.; De-Beer E. J. **Fed. Proc.** *1959*, 18, 412.